Remarks

Upon entry of the foregoing amendment, claims 112, 115-126 and 129-134 are pending in this application. Claims 1-111 have been previously cancelled without prejudice or disclaimer. Claims 113, 114, 127 and 128 are newly cancelled herein without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the cancelled claims (1-111, 113, 114, 127 and 128) either in a continuing or divisional application without prejudice or disclaimer. Claims 112, 120, 122, 125 and 132 are newly amended.

Support for the amendments to claim 112 are found, for example, on page 4, lines 15-25; page 5, lines 25-26 ("In addition to antigen and adjuvant, the formulation may comprise a hydrating agent (e.g., liposomes).. .")(emphasis added); page 20, lines 31-33 ("Although not required to practice the instant invention, hydration .....of the stratum corneum may be enhanced by adding liposomes to the formulation."); and, Example 17 (disclosing an immunization procedure wherein the skin was not treated with saline before administration of the antigen-adjuvant solution). It is again noted for the record that hydrated skin is a merely a variation of the invention described herein and is not a critical limitation.

Currently amended claim 112 does not require the term "hydrated" for patentability and the term has been deleted. A review of the prosecution history indicates that claim 69 was added and included the phrase "hydrated" in the Reply under 37 CFR § 1.116, filed Dec. 31, 2001. In reply (Reply, July 18, 2002) to the restriction requirement, Applicants noted that claim 78 (including the term "hydrating") should be included in the restriction grouping because "hydrating" was a variation of the invention described in the specification. In the Office Action dated October 18, 2002, the Office commented (Office Action, page 6, first full paragraph) "Note that the specification discloses exclusively the use of a group of closely related adjuvants referred to as ADP ribosylating exotoxin adjuvants or bAREs on hydrated skin." Contrary to the allegations of the Office, Example 17, page 46, discloses application of CT (a bARE) on nonhydrated skin.

Although the Office withdrew a 35 U.S.C. § 103 rejection after claim 1 and other independent claims were amended to include the word "hydrated," (Applicants amended the claims to concur with the Examiner's implicit suggestion to do so, Reply, March 18, 2003)), Applicants assert that currently amended claims 112 and 132 are free of the prior art and the word "hydrated" is not needed for patentability. The Office statement in the June 2, 2003, Office Action (stating "application of instant formulation to hydrated skin" rejections based on Paul *et al.* have been withdrawn because the reference teaches the application of the immunizing solution to dry skin) misses the reason why Paul *et al.* is not prior art to the claim. Paul *et al.* (Paul *et al.*, Eur. J. Immunol. 25: 3521 (1995))("Paul 1995") discloses the use of transferosomes. Transferosomes are not liposomes (Paul 1995, page 3521, left column, second paragraph, distinguishing the differences between transferosomes and liposomes). Whether Paul 1995 applies the transferosome formulation to dry skin or hydrated skin is irrelevant to a claim claiming, *inter alia*, an effective amount of an antigen which is not encapsulated by lipsomes. Thus the Paul 1995 document cannot, and does not, teach or suggest the invention claimed in newly amended claim 112.

Domb is cited by the Office (Office Action, Dec. 7, 2000) for allegedly teaching "applying a formulation to intact skin of an organism, wherein the formulation comprises liposomes and the antigen.... and wherein the formulation further contains an adjuvant... ." (Office Action, page 4, paragraph 19). However, contrary to the Office arguments, Domb teaches the application of lipospheres. Liposphere are not liposomes (column 7, lines 37-40: "The lipospheres are distinct from microdroplets, vesicles or liposomes since the lipospheres have solid inner cores at the temperature at which they are used (usually body temperature)."). Domb further discloses (column 1, lines 64-65) that "They (liposomes) are difficult to prepare, unstable, and can only be used for encapsulation of certain types of materials." Domb teaches the advantages of lipospheres, saying that "The resulting lipospheres have several advantages over other delivery systems, including emulsions, vesicles and liposomes." Thus, Domb clearly teaches away from the use of liposomes and does not teach or suggest, *inter alia*, a method for inducing an immune

response by applying a formulation comprising an effective amount of an antigen not encapsulated by liposomes.

Other prior art documents cited (Office Action, Dec. 7, 2000) in the 35 U.S.C. § 103 rejections (Domb, USPN 5,340,588 ("Domb"); Marinaro *et al.*, J. Immunol. 155: 4621 (1995) ("Marinaro"); Kosecka *et al.*, Am. J. Physiol. 267: G745 (1994)("Kosecka") and Wille *et al.*, USPN 5,686,100 ("Wille")) do not cure the deficiencies of either the Domb or Paul 1995 documents. Kosecka is cited by the Office for the teaching that "pertussin toxin enhances nerve mediated uptake in intestines" (Office Action, page 6, lines 1-2). Marinaro is cited by the Office for the teaching that cholera toxin (CT) has become a model mucosal immunogen and adjuvant because microgram quantities of cholera toxin induces significant IgG antibodies and these responses are major histocompatibility complex restricted (Office Action, page 5, paragraph 23). Wille is cited by the Office for teaching a patch for transcutaneous or transdermal delivery of drugs that comprises a protein antigen (Office Action, page 6, top paragraph). Since no document, taken alone or together, suggests *inter alia*, an effective amount of an antigen which is not encapsulated by lipsomes, as claimed in newly amended claim 112, claim 112 is free of the prior art and patentable thereover.

Claim 120 was amended to delete the phrase "tumor necrosis factor alpha" and the phrase is the subject of new claim 134. Claim 122 was amended to correct a grammatical error. Claim 132 was amended to more clearly claim the invention. The deleted phrase is considered to be redundant to the type of formulation used. Claim 134 is newly added herein in direct response to the Examiner's suggestion to do so. Support for the amendments to claim 125 are found, for example, on page 18, lines 1-6. Claims 112-126 and 129-134 are currently under examination. Claims 112 and 132 are the independent claims.

No new matter is believed to have been added by this amendment. In view of the amendments and following remarks, reconsideration of the rejections and withdrawal thereof is respectfully

requested.

The Final Office Action dated March 17, 2004 has been carefully reviewed and the foregoing amendments are made in response thereto.

Rejection of claims 117, 123, 125 and 127 under 35 U.S.C. § 112, first paragraph

The Office rejected claims 117, 123, 125 and 127 under 35 U.S.C. § 112, first paragraph, in that the disclosure allegedly does not reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The Office asserts the specification and claims as originally filed do not provide support for the invention as claimed in claims 117, 123, 125 and 127. Claim 127 has been cancelled without prejudice or disclaimer. The rejections are respectfully traversed.

A. In particular, the Office asserts the phrase "live virus" (claim 117) does not find support in the specification. However, support for the phrase "live virus" is explicitly found on page 6, lines 10-11 ("Alternatively, antigen may be provided in the form of a **live virus**... .") (emphasis added); on page 19, lines 2-3 ("It is envisioned that whole cell preparations, **live viruses**, attenuated viruses... .")(emphasis added); and, elsewhere throughout the specification.

B. The Office alleges that support is only found (claim 123) for the B subunit of cholera toxin. However, contrary to the allegations, support for B subunits for other ADP-ribosylating exotoxins is found, for example, on page 16, line 23 through page 17, line 10; page 16, lines 4-11 ("Most bARe's are organized as A:B dimer with a binding B subunit and an A subunit containing the ADP-ribosyltransferase. Such toxins include diphtheria, *Pseudomomas* exotoxin A, cholera toxin (CT), *E. coli* heat labile entertoxin (LT), pertussis toxin, *C. botulinum* toxin C2 *C. botulinum* toxin C3, *C. limosum* exoenzyme, *B. cereus* exoenzyme, *Pseudomonas* exotoxin S *Staphylococcus aureus* EDIN and *B. sphaericus* toxin); on page 34, lines 19-30, showing support for the B subunit of LT (heat labile enterotoxin); and, elsewhere throughout the specification.

As disclosed in the specification, LT and CT are members of the family of bacterial ADP-ribosylating exotoxins (bAREs). Both LT and CT are organized as A:B proenzymes with the ADP-ribosyltransferase activity contained in the A subunit and the target cell binding a function of the B subunit. LT is 80% homologous with CT at the amino acid level and has a similar non-covalently bound subunit organization, stoichiometry, the same binding target and size similarity (MW approximately 80,000) as CT. The similarities of LT and CT appear to influence their immunogenicity as reflected by the similar magnitude of antibody response (Table 1, page 32 and Table 3, page 34). Other bAREs are known to have structural similarities to both LT and CT. See, specification page 16, lines 3-11 (discussed above) disclosing the structural similarities between bAREs. Thus, contrary to Office arguments, support for the B subunit from other bAREs is found within the specification.

C. The Office alleges that support is not found for claim 125. Claim 125 is newly amended herein (see, above) and is set forth below for convenience:

> 125. The method of claim 112, wherein the formulation comprises an adjuvant selected from the group consisting of an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated; an ADP-ribosylating exotoxin chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; an ADP-ribosylating exotoxin subunit chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; and, an ADP-ribosylating toxoid chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen.

Contrary to the assertions of the Office, literal support for the italicized phrases in claim 125, set forth below:

> 125. The method of claim 112, wherein the formulation comprises an adjuvant selected from the group consisting of an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated; an ADP-ribosylating exotoxin *chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen;* an ADP-ribosylating exotoxin subunit *chemically conjugated* to a *carbohydrate, polypeptide, glycolipid, or glycoprotein antigen;* and, an ADP-ribosylating toxoid *chemically conjugated* to a *carbohydrate, polypeptide, glycolipid, or glycoprotein antigen*.

is found on page 18, lines 1-6, wherein it is stated "The bARE adjuvant may be *chemically conjugated* to other antigens including, for example, *carbohydrates*, *polypeptides*, *glycolipids* and *glycoprotein antigens*." It is clear from the foregoing that claim 125 has literal support in the specification for the italicized phrases.

Further, literal support for the concept of chemical conjugation of toxins, toxin subunits and toxids to those antigens (*carbohydrates*, *polypeptides*, *glycolipids* and *glycoprotein antigens*) as claimed in claim 125 (bolded phrases), set forth below:

> 125. The method of claim 112, wherein the formulation comprises an adjuvant selected from the group consisting of an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated; **an ADP-ribosylating exotoxin** chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; **an ADP-ribosylating exotoxin subunit** chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; and, **an ADP-ribosylating toxoid** chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen.

is also explicitly found in the specification on page 18, lines 1-6, wherein it is stated "Chemical

conjugation with **toxins**, their **subunits** or **toxoids** with these antigens... ." "These antigens" are the carbohydrates, polypeptide, glycolipids and glycoprotein antigens referred to in the first three lines of the first paragraph (lines 1-6) on page 18. Thus, it is clear from the foregoing that the bolded phrase set forth below:

> 125. The method of claim 112, wherein the formulation comprises an adjuvant selected from the group consisting of an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated; **an ADP-ribosylating exotoxin chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; an ADP-ribosylating exotoxin subunit chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; and, an ADP-ribosylating toxoid chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen.**

within amended claim 125 has literal support in the specification on page 18, lines 1-6.

Finally, support for the italicized phrase in newly amended claim 125, set forth below:

> The method of claim 112, wherein the formulation comprises an adjuvant selected from the group consisting of *an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated*; an ADP-ribosylating exotoxin chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; an ADP-ribosylating exotoxin subunit chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen; and, an ADP-ribosylating toxoid chemically conjugated to a carbohydrate, polypeptide, glycolipid, or glycoprotein antigen.

is found on page 18, lines 12-15, wherein it is stated:
"This is based on inactivating the catalytic activity of the ADP-ribosyl transferase by genetic

deletion. These toxins retain the binding capabilities, but lack the toxicity, of the natural toxins."

Thus, support for the phrase *an ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated* is found within the specification. That the catalytic activity of the ADP-ribosylase exotoxin is a transferase activity is taught on page 16, lines 17-21, and elsewhere throughout the specification.

In summary, support for amended claim 125 has been amply demonstrated as set forth above and elsewhere throughout the specification.

D. The Office alleges that support is not found (claim 127) for the phrase "more than one draining lymphnode field." Claim 127 is newly cancelled herein without prejudice or disclaimer in order to expedite prosecution and allowance. However, contrary to the assertions of the Office, support for the phrase is found on page 7, lines 9-13; page 5, lines 13-16; and, elsewhere throughout the specification.

Thus, in view of the amendments to the claims and arguments herein, it is believed the rejections are moot and can be withdrawn. Reconsideration and withdrawal of the rejections is respectfully requested.

Rejection of claim 120 under 35 U.S.C. § 112, second paragraph

The Office rejected claim 120 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctively claim the subject matter which applicant regards as the invention. In particular, claim 120 is alleged to be indefinite for comprising an improper Markush group. The rejection is respectfully traversed.

Without acquiescing to the propriety of the rejection, claim 120 has been amended to delete the phrase "tumor necrosis factor alpha." The deleted subject matter is now claimed in new claim

134 at the suggestion of the Examiner. In view of the amendment to claim 120, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under the Judicially Created Doctrine of Obviousness Type Double Patenting

The Office provisionally rejected claims 112-133 under the judicially created doctrine of obviousness type double patenting as being:

1) unpatentable over claim 2 of copending application no 10/633,626;
2) unpatentable over claims 32 and 33 of copending application no. 10/701,069; and,
3) unpatentable over claim 17 of copending application no. 10/435,676.

The rejections are respectfully traversed. As the Office is aware, once the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the rejection should be withdrawn and the application permitted to issue as a patent (MPEP § 804 (I)(B), page 800-19, February 2003). In view of the amendments to the claims and cancellation of other claims, it is believed the provisional rejections are the only rejections remaining in this application. Reconsideration and withdrawal of the provisional rejections is respectfully requested.

Other Matters

Applicants note that an executed PTO 1449 form, filed at the US PTO with an IDS on February 17, 2004, has not been returned with the Final Office Action. It is further noted, however, that two copies of a signed, dated and initiated PTO 1449 form, filed with an IDS on January 27, 2004, have been returned. Although presumably the February 17 IDS has been considered by the Examiner, Applicants nevertheless submit herewith a clean copy of the February 17, 2004 IDS, PTO 1449 form, copy of each listed document and a copy of the date stamped receipt post-card showing receipt by the PTO of the IDS, PTO 1449 form and copies of the listed documents. If the Examiner has not previously considered the February 17, 2004 IDS, the Examiner is

respectfully requested to consider each cited document and to return an initialed, signed and dated PTO 1449 form to Applicants with the next communication in this application.

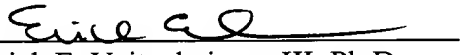
Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. If, in the opinion of the Examiner, an interview would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the telephone number provided below.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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